Remarks

Please cancel claims 30-41, 44-48 and 51 without prejudice or disclaimer. Claims 28, 29, 42, 43, 49 and 50 are pending. Claims 28, 29, 42, 43, 49 and 50 have been rejected on various grounds. In this response, applicants amend claims 28, 29, 42, 43, 49 and 50 and provide arguments against the remaining rejections. Reconsideration and allowance are requested.

Claim Rejections

Definiteness Rejections

The Examiner rejects claims 28, 29, 42, 43, 49 and 50 on pages 2-5 of the Office Action on indefiniteness grounds.

For definiteness, a claim need only reasonably apprise those skilled in the art of the utilization and scope of the invention. *Hybritech, Inc. v. Monoclonal Antibodies,* 231 USPQ 81, 94-95 (1986). Words are to be given their plain meaning as understood by the person of ordinary skill in the art, particularly given the limitations of the English language. *See* MPEP §§ 707.07(g); 2111.01 (August 2001). Claims are to be given their broadest reasonable interpretation consistent with the specification. *See* MPEP § 2111 (August 2001). In sum, in order to reject the claims on definiteness grounds, it is incumbent on the Examiner to show how and why the skilled person having applicants' specification would not be apprised of the invention by the language-at-issue. The rejections are discussed below.

a) The Examiner asserts that the phrase "as the only structurally and functionally intact SCR domains of CR1" "is confusing". The Examiner also opines that "it is unclear what relationship CR1 has to the claimed polypeptide". In response, Applicants amend the claim by deleting the phrase to avoid confusion.

b) The Examiner objects to the phrase "wherein at least one of the native amino acids is substituted" in one or more of the above mentioned claims. In response, Applicants have amended the claims to include SCR and add sequence identifiers to the claims.

c) On page 4 of the Office Action, the Examiner states that the "positions of the proposed amino acid substitutions are indefinite". In response, Applicants point out that the substitutions are in relation to the native CR1 sequence starting at SCR1. Applicants further refer to pages 4-5 of the specification, SEQ ID NO: 58 and SEQ ID NO: 59 (see amendment and sequence listing filed on June 12, 2000), wherein the sequence positions are clearly described. Furthermore, Applicants amend claims and add SEQ ID NOs to provide further clarity.

d) The Examiner rejects claims 42, 43 and 49 for using the term "derivatives". In response the Applicants point out that the "derivatives" are the polypeptides comprising SCRs, which are well known in the art (see, for example, US Patent No. 5,833,989 and 5,859,223), as set forth in SEQ ID NO: 59 with at least one of the listed substitutions (see for example SEQ ID NO: 58). Applicants are willing to replace term with any other relevant term the Examiner may suggest for additional clarity. Applicants further point out that the term "derivatives" is defined and described on page 11 lines 21-29 and discussed therein. Additionally, Applicants amend claims and include SEQ ID NOs. Therefore, one of ordinary skill in the art would reasonably appraise of the metes and bounds of the invention.

g) The Examiner states that in claim 42 the term 'thermodynamic additivity' renders the claim indefinite. In response, Applicants respectfully disagree with the Examiner and point out that the term has been well known to one skilled in the art and has been in practice (See, for example, page 699, paragraph 1, lines 1-4, in Murphy and Gill. J. Mol. Biol. 222(3):699-709 (1991)). Additionally, Applicants provide a review article of Dill KA, J. Biol. Chem. 272(2):701-704 (Issue of January 10, 1997), wherein 'additivity principles in biochemistry' and more specifically 'thermodynamic additivity' is discussed.

j) Applicants amend the claims following the Examiner's suggestion and add sequence identifiers, as applicable, so that the metes and bounds of the claims can be ascertained.

Written Description Rejections

On pages 5-7 of the Office Action, the Examiner has rejected claim 43 for written description of polypeptide derivatives. The Examiner alleges that "the specification discloses a

polypeptide of SEQ ID NO: 1, yet the claim encompasses polypeptide derivatives not described in the specification".

The USPTO issued its final guidelines for written description (66 Fed. Reg. 1099) in early 2001. The written description guidelines first instruct examiners to determine what the claim as a whole covers and then review the entire specification to determine whether all subject matter that is essential to the invention is actually recited in the claims. See written description guidelines at II(A)(1), (2). Next, the examiners are instructed to determine whether the applicant was in possession of all that is claimed. See the written description guidelines at II(A)(3). According to the guidelines, possession of a claimed invention can be shown by disclosure of structural characteristics, functional characteristics that correlate with structure or combinations thereof. See the written description guidelines at II(A)(3)(a). Claims that encompass a genus must be supported by a written description of a representative number of species. See the written description guidelines at II(A)(3)(a)(2). The written description of the representative species of the genus can be shown by disclosure of structural characteristics, functional characteristics that correlate with structure or combinations thereof. Applicants submit that the examiner has not satisfied these guidelines in making the rejection, which alone is grounds for withdrawal of the rejection.

Nevertheless, Applicants herein demonstrate that the structural requirements set forth in claim 43 find correspondence in the specification. Applicants submit that it is clear that they had possession of the subject matter claimed in claim 43. Given the correspondence and applicants' identification of this correspondence, a heavy burden is placed upon the examiner to reject the claims. *See* MPEP § 2163.04 (August 2001). For example, applicants point out that the specification describes additional derivatives of membrane binding sequences, in addition to SEQ ID NO: 1, SEQ ID NO: 59 and descriptions on pages 10 and 11 of the specification. The specification also cites references (see, for example, Blackshear. J. Biol. Chem. 268:1501-1504 (1993)) as sources where further examples of suitable membrane binding elements and amino acids sequences can be found (see pages 10-11).

Thus, withdrawal of the written description rejection is solicited.

Obviousness Rejections

On page 7-8 of the Office Action, the Examiner has rejected claims 28, 29, and 50 as obvious over US Patent No. 5,545,619 in combination with Hourcade *et al.*, J. Biol. Chem. 265(2):974-980 (1990). The Examiner alleges that "U.S. Patent No: 5,545,619 teaches a soluble polypeptide (CR1) comprising one to four short consensus repeats [SCR] of the long homologous repeat A (LHR-A) and related polypeptides termed RCA polypeptide (see col 6), methods of producing mutations in said polypeptides (see col 7), and pharmaceutical compositions containing therapeutically effective amounts of same (see col. 9)".

At the outset, applicants note the Examiner must show all of the recited claim elements in the combination of references that make up the rejection. When combining references to make out a *prima facie* case of obviousness, the Examiner is obliged to show by citation to specific evidence in the cited references that (i) there was a suggestion/motivation to make the combination and (ii) there was a reasonable expectation that the combination would succeed. Both the suggestion/motivation and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *W.L Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir. 1983) (holding that is improper in combining references to hold against the inventor what is taught in the inventor's application); *see also* MPEP §§ 2142-43 (August 2001). Thus, the Examiner must provide evidentiary support based upon the contents of the prior art to support all facets of the rejection, rather than just setting forth conclusory statements, subjective beliefs or unknown authority. *See In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002).

When an examiner alleges a *prima facie* case of obviousness, such an allegation can be overcome by showing that (i) there are elements not contained in the references or within the general skill in the art, (ii) the combination is improper (for example, there is a teaching away or no reasonable expectation of success) and/or (iii) objective indicia of patentability exist (for example, unexpected results). *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); *Gillette Co. v. S.C.*

Johnson & Son, Inc., 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 419-20 (Fed. Cir. 1986).

Natural allelic variation vs. purposeful mutation:

Applicants respectfully traverse the rejections and reiterate that at the time of the filing of instant application CR1 and its SCR components were known to skilled artisan and the present invention teaches non-obvious mutations made in CR1 and its SCR components, which is not in the teachings of US Patent No. 5,545,619 nor Hourcade *et al.* In contrast, U. S. Patent No. 5,545,619, in combination with Hourcade *et al.*, concerns CR1 diversity or natural allelic variations rather than purposeful mutation and substitutions as set forth in the claims of the instant application. At the time of the invention, SCR components of CR1 were known as active polypeptide fragments and it was not obvious to skilled artisan that mutations made in SCR domains would not render the polypeptide inactive.

Purposeful mutation is set forth in claims:

In addition, the Examiner states, on page 8 of the office action that "no claims require that mutations be in SCR3". In response, the Applicants amend the claims clearly indicating purposeful mutation in at least one of SCR sequences. The amended claim 28 states "including at least SCR3, wherein at least one of the native amino acids of the SCR (SEQ ID NO: 59) is substituted".

'col. 6, lines 6-15' of Hourcade et al. does not describe mutation:

The Examiner states that "U.S. Patent No: 5545619 teaches that the mutations disclosed by Hourcade *et al.* are encompassed by the invention of U.S. Patent No: 5545619 (see col. 6, lines 6-15)". Applicants respectfully disagree with the Examiner's interpretation of the prior art U.S. Patent No: 5,545,619 and reiterate as above that the prior art does not teach purposeful mutation. Applicants point out that 'col. 6, lines 6-15' of Hourcade *et al.* has no description or discussion of 'mutation' of sequences set forth in the claims of the instant application. Applicants also point out that Hourcade *et al.* describes natural variations in CR1, which does not describe

or provide indication to any of the purposeful mutations in SCR domains of CR1 as described in the instant application and recited in the claims.

In response to the Examiner's statement on page 8 on "RCA proteins" and reference to Hourcade *et al.*'s "col. 6, lines 6-15", and "the last paragraph of col. 8" the Applicants further refers to the arguments made above and point out that the referred citations do not teach polypeptides of the current invention encompassing mutations/substitutions in CR1 SCR domains.

'col. 7' of Hourcade et al. does not describe methods of purposeful mutation as set forth in instant claims:

The Examiner further states that the methods of producing mutations is described in Hourcade *et al.* and referred to "(see col 7)". The Applicants respectfully disagree with the Examiner's interpretation of the "col 7". First, the Examiner did not specify the line numbers where such methods are disclosed. Secondly, the "col 7" lines 11-67 describes recombinant techniques to obtain an analog and expression of the system. The "col 7" does not describe any methods of purposeful mutation as described in the instant application and recited in the claims.

Applicants further point out that Hourcade *et al.* discloses diversity between the wild-type CR1 amino acids sequence and the CR1-like predicted sequences. There are 39 CR1-like predicted sequences (As shown on Figure 3), but Hourcade *et al.* do not teach which one is compatible with retention of activity in multi-SCR constructs; none of which were expressed or assayed in prior to the filing of this application. In fact, prior to the current invention, no domain of the CR1-like gene was expressed and studied. In the col. 6, lines 6-15 of the U.S. Patent No. 5,545,619, it is clearly described that "it is unclear whether this [CR1 gene] sequence is expressed". Therefore, it would not have been obvious to design a construct such as CM7 (for example, SEQ ID NO: 1 or SEQ ID NO: 58). Thus, at the time the invention was made, there would have been no "reasonable expectation of success," to produce polypeptides of current invention "having the amino acid sequence taught by Hourcade *et al.* when practicing the invention disclosed in the U.S. Patent No: 5,545,619."

On page 10-11 of the Office Action, the Examiner rejects claims 43 and 49 allegedly as being unpatentable over US Patent No. 5,545,619 in view of Hourcade *et al.*, *J. Biol. Chem.* 265(2):974-980, 1990, as applied to claims 28, 29, 42 and 50 and in further view of Clissold *et al.*, *Eur. J. Immunol.* 23:2346-2352, 1993 and U.S. Patent No: 5,936,092, as indicated previously in item 10 of Paper 14. The Examiners asserts that "Clissold *et al.* teach that the addition of a membrane binding element to soluble CR1 increases the effectiveness of CR1". In response, the Applicants traverse the rejections and refer to arguments made in preceding paragraphs. Applicants again point out, at the time the invention was made, it was non-obvious to obtain an active polypeptide as a result of the recited mutations in SCR domains of CR1. Thus, there would be no motivation to add membrane binding elements, based on the teaching of Clissold *et al.*, to the SCR elements to increase the effectiveness.

Applicants therefore submit that the Examiner has not established a *prima facie* case of obviousness, and therefore respectfully request withdrawal of the rejection.

In addition, for further clarity, the Applicants amend the claims 28, 29, 42, 43 and 50. The amendment should satisfy the Examiner's objection. Withdrawal of the rejection is respectfully requested.

Anticipation Rejection

On page 12 of the Office Action, the Examiner rejected claim 43 for the suggested amendment to the claim made in response to previous office action (paper no. 14), as being anticipated by U.S. Patent No: 5,936,092. In response, the Applicants appreciate the Examiner's suggestion and have amended the claim 43 to recite a soluble derivative, thereby obviating the rejection. Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the foregoing remarks, reconsideration of the application and allowance of all claims are requested. If there are any issues remaining which the Examiner believes could be

resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the local exchange listed.

Respectfully submitted,

Date: March 28, 2002

John P. Isacson
Attorney for Applicant
Reg. No.: 33,715

Heller Ehrman White & McAuliffe LLP
1666 K Street, N.W., Suite 300
Washington, D.C. 20006-4004
Telephone: (202) 912-2000
Facsimile: (202) 912-2020

Customer No. 26633

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MARKED UP COPY OF AMENDED CLAIMS

28. A soluble polypeptide comprising in sequence [one to four] three short consensus repeats (SCR) of long homologous repeat A (LHR-A) selected from the group consisting of SCR 1, 2, 3, and 4, [as the only structurally and functionally intact SCR domains of CR1] and including at least SCR3, wherein at least one of the native amino acids of the SCR (SEQ ID NO: 59) is [are] substituted, wherein the substitution[s are] is selected from the group consisting of Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, and His at position 236.

29. The polypeptide according to claim 28 that comprises SCR selected from the group consisting of SCR 1, 2, 3 and 4 of LHR-A or SCR 1, 2 and 3 of LHR-A [as the only structurally and functionally intact SCR domains of CR1].

42. A soluble derivative of a soluble polypeptide (SEQ ID NO: 59), wherein said soluble derivative comprises in sequence [one to four] three short consensus repeats (SCR) of long homologous repeat A (LHR-A) selected from the group consisting of SCR 1, 2, 3, and 4, [as the only structurally and functionally intact SCR domains of CR1] and including at least SCR3, wherein at least one of the native amino acids of the SCR (SEQ ID NO: 59) is [are] substituted, wherein the substitution[s are] is selected from the group consisting of Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, His at position 236,

wherein said soluble polypeptide comprises at least two heterologous membrane binding elements with low membrane affinity covalently associated with the polypeptide, wherein the elements are capable of interacting independently and with thermodynamic additivity with components of cellular membranes exposed to extracellular fluids,

wherein the membrane binding elements have an affinity with a dissociation constant of between at least about 1μM and 1mM.

43. The soluble derivative of polypeptide according to claim 42, comprising two to eight membrane binding elements selected from the group consisting of fatty acid derivatives, ligands of internal membrane proteins, sequences derived from the complementarity-determining region of monoclonal antibodies raised against epitopes of membrane proteins, and membrane binding sequences identified through screening of random chemical libraries.

49. A process for preparing a soluble derivative of a soluble polypeptide (SEQ ID NO: 59), wherein said soluble derivative comprises in sequence [one to four] three short consensus repeats (SCR) of long homologous repeat A (LHR-A) selected from the group consisting of SCR 1, 2, 3, and 4, [as the only structurally and functionally intact SCR domains of CR1] and including at least SCR3, wherein at least one of the native amino acids of the SCR (SEQ ID NO: 59) is [are] substituted, wherein the substitution[s are] is selected from the group consisting of Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, His at position 236, comprising

expressing DNA encoding the polypeptide portion of said derivative in a recombinant host cell and recovering the product and thereafter post translationally modifying the polypeptide to chemically introduce membrane binding elements.

50. A pharmaceutical composition comprising (A) a therapeutically effective amount of a soluble polypeptide comprising in sequence [one to four] three short consensus repeats (SCR) of long homologous repeat A (LHR-A) selected from the group consisting of SCR 1, 2, 3, and 4, [as the only structurally and functionally intact SCR domains of CR1] and including at least SCR3, wherein at least one of the native amino acids of the SCR (SEQ ID NO: 59) is [are] substituted, wherein the substitution[s are] is selected from the group consisting of Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, His at position 236, and (B) a pharmaceutically acceptable carrier or excipient.